REMARKS

Claims 205-209, 211-217, 219-226, and 228-231 are pending in the application. Claims 219-223 are withdrawn as being drawn to non-elected inventions. Claims 205-209, 211-217, 224-226, and 228-231 are under consideration. Claims 207 and 216 have been canceled. The present amendment does not introduce new issues, and places the subject application in condition for allowance and/or simplifies issues for appeal. Accordingly, entry of the amendment is proper and respectfully requested. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

Rejoinder

Applicants thank the Examiner for rejoining claims 205-209, drawn to polypeptides, with the claims of Group II. Applicants reiterate their request that claims 219-223, drawn to methods of using the polynucleotides, be rejoined, and in addition, request that claims 208 and 209, drawn to methods of using the polypeptides, be rejoined per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants request that claims 219-223 be rejoined and examined upon allowance of the claims drawn to the polynucleotides of Group II and that claims 208 and 209 be rejoined and examined upon allowance of the claims drawn to the polypeptides.

Objection to the Title

The title has been revised as suggested by the Examiner to reflect the election of claims directed to polynucleotides and polypeptides. Withdrawal of the objection to the title is therefore respectfully requested.

Objections to the Claims

Claims 207 and 216 have been canceled; therefore, the objections to these claims are moot.

Utility Rejections under 35 U.S.C. §101 and §112, First Paragraph

Claims 205-209, 211-217, 224-226, and 228-231 have been rejected under 35 U.S.C. §101 and §112, first paragraph, for alleged lack of utility. These rejections are traversed for the reasons already made of record in the response to the Office Action of January 10, 2003, the Declaration of Dr. Tod Bedilion, and on the following grounds.

I. Response to Specific Arguments of the Examiner Regarding Utility of the Claimed Polynucleotides

The Examiner alleges that the specification does not disclose whether the polynucleotide of SEQ ID NO:64 is differentially expressed in different cells or tissues, and therefore "the gene is not a disease marker or an appropriate target for drug discovery or toxicology testing" (Final Office Action at pages 3-4). However, Applicants need not demonstrate whether the polynucleotide is differentially expressed, only whether it is useful.

The Examiner erroneously states that "the determination of tissue expression appears to have been conducted using only a fragment of 45 nucleotides (nucleotides 489-533) of the nucleic acid of SEQ ID NO:64" (Final Office Action, page 4). This is incorrect. Column 2 of Table 3 lists fragments of the polynucleotide sequences of column 1 that may be useful, for example, in "hybridization or amplification technologies" to identify the claimed polynucleotides and to distinguish them from related polynucleotide sequences (See specification at page 26, lines 11-15). The expression analysis, however, was not restricted to a single fragment. Rather, the tissue distribution was determined, as described on page 62 of the specification, based on the tissue of origin of numerous cDNA sequences from the LIFESEQ database. The different cDNAs used in the analysis in combination cover the full length of SEQ ID NO:64. Expression was detected in reproductive, gastrointestinal, and nervous system tissues, though the Examiner is correct in noting that expression was not found exclusively in these tissues.

The Examiner further questions whether Applicants have identified the specific reproductive, gastrointestinal, and nervous system tissues where the polynucleotide of SEQ ID NO:64 is expressed. This is information the Examiner feels is "necessary for a real world use for the claimed nucleic acid"

(Final Office Action, page 4). Indeed, specific tissues were identified as shown in Exhibit A, which lists cDNA libraries from which clones matching SEQ ID NO:64 (Incyte ID 2615168) were isolated.

The Examiner alleges that "the specification fails to disclose the methods and information necessary for a skilled artisan to use the claimed polynucleotide for toxicology testing" (Final Office Action, page 15). However, well established uses, such as toxicology testing and drug screening, need not be explicitly described in the specification. The instant application claims priority to United States Provisional Patent Application, Serial No. 60/139,566, filed on June 16, 1999, (hereinafter "the Yue '566 application"). The Yue '566 application recites that "[t]herapeutic efficacy and **toxicity** may be determined by standard pharmaceutical procedures" (Yue '566 application, page 30, lines 7-8; emphasis added). Also, the Yue '566 application recites that polynucleotides which encode the claimed polypeptides can be included on a microarray that "can be used to monitor the expression level of large numbers of genes," and this information may be used "to develop and monitor the activities of therapeutic agents" (Yue '566 application, page 34, lines 11-15).

Furthermore, the Declaration of Dr. Tod Bedilion demonstrates that toxicology testing was a well-established utility at the time both the present application and the Yue '566 application were filed. In that regard, the Bedilion Declaration describes the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time the patent application was filed. The Bedilion Declaration, at ¶ 10, specifically discusses how the teachings of the Yue '566 application clearly include using differential gene expression analyses in toxicity and drug evaluation studies. In particular, ¶ 10 states that "[t]he Yue '566 application discloses that the polynucleotide sequences disclosed therein, including the SEQ ID NO:12-encoding polynucleotides, are useful as probes in microarrays." It further teaches that the microarrays can be used "to monitor the expression level of large numbers of genes simultaneously" for a number of purposes, including "to develop and monitor the activities of therapeutic agents." ¶ 10 goes on to discuss how the Yue '566 application teaches that microarrays can be prepared using the previously mentioned cDNA microarray technology developed at Stanford in the early to mid-1990s, and in particular cites the Schena 1996 (reference (a) of the Bedilion Declaration) as one of a number of documents that were published prior to the June 16, 1999 filing date of the Yue '566 application that describes the use of the Stanford-developed cDNA technology in a wide range of gene expression monitoring applications, including

monitoring and analyzing gene expression patterns in human cancer. Thus the Yue '566 application specifically teaches toxicity testing and drug discovery using the encoding polynucleotides of the invention.

Also contrary to the Examiners assertion (Final Office Action, pages 3-4), there need not be a well established or disclosed correlation between the claimed polynucleotide and a disease or disorder in order for a polynucleotide to be useful in disease diagnosis. Applicants respectfully submit that the claimed polynucleotides are useful whether or not the claimed polynucleotides are associated with disease. Each individual sequence has a utility in creating arrays. Each sequence has a unique and specific utility in that it records the expression level of a unique gene or protein. This is a substantial, "real world" utility in that one of ordinary skill in the art would know how to use the claimed sequences in an array without any further experimentation.

If a drug candidate, targeted to a polynucleotide other than the claimed polynucleotide or targeted to a polypeptide other than the polypeptide encoded by the claimed polynucleotide, alters expression of the claimed polynucleotide, that drug candidate is considered to have an undesirable side effect. As Dr. Bedilion explains in his declaration, good drugs "have strong effects on a specific biological target and minimal effects on all other biological targets" (Bedilion Declaration, ¶ 10). Disruption of the expression of a polynucleotide which is not the target of a drug candidate is, therefore, an undesired side effect of that drug candidate. Measuring the expression level of the claimed polynucleotide, such as during a toxicology test of a drug candidate targeted to another polynucleotide, would **not** require knowledge of the biological function or disease association of the claimed polynucleotide, as the Office Action would have it.

Furthermore, in toxicology testing, every distinct polynucleotide expressed in humans has utility based solely on the property of being expressed in humans. However, the results obtained from using any particular human-expressed polynucleotide in toxicology testing is **specific to both the compound being tested and the polynucleotide used in the test**. No two human-expressed polynucleotides are interchangeable for toxicology testing because the effects on the expression of any two such polynucleotides will differ depending on the identity of the compound tested and the identities of the two polynucleotides. Therefore, the asserted utility of the claimed polynucleotide for toxicology testing is

specific to that particular polynucleotide, as well as substantial, and so more than adequately satisfies the statutory requirements for utility.

The Examiner also asserts that the utility of the claimed polynucleotides in toxicology testing is not specific because "[i]f any polynucleotide expressed in a human has utility in toxicology testing, then that polynucleotide has no specific utility as all polynucleotides would have such use" (Final Office Action, page 6). The Examiner does not point to any law, however, that says a utility that is shared by a large class is somehow not a utility. If all of the class of polypeptides or polynucleotides can be so used, then they all have utility. The property of the claimed polynucleotides that makes them useful as a control for toxicology testing is their expression in naturally occurring cells. A polynucleotide having a random, non-naturally occurring sequence would most likely not be useful as a control for toxicology testing. The issue is, once again, whether the claimed invention has any utility, not whether other compounds have a similar utility. Nothing in the law says that an invention must have a "unique" utility. Indeed, the whole notion of "well established" utilities presupposes that many different inventions can have the exact same utility. If the Examiner's argument was correct, there could never be a well established utility, because you could always find a generic group with the same utility!

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the annexin family, the Examiner contends that membership in the annexin family does not establish utility. Applicants attach the Nguyen *et al.* article to this Response as Exhibit B (J. Biol. Chem. (2000) 275:29466-29476). This article corroborates that the polypeptide of SEQ ID NO:12 is a member of the annexin family and is, in fact, the human keratinocyte annexin-like protein, Pemphaxin. Pemphaxin is is 99.7% identical to SEQ ID NO:12 (see Exhibit C). Pemphaxin acts as a cell surface cholinergic receptor involved in the regulation of keratinocyte cell adhesion and known to be associated with the autoimmune disorder, pemphigus vulgaris. This is a powerful demonstration of the effectiveness of sequence homology in the assignment of biological function.

Furthermore, Nguyen et al. identified pemphaxin in a screen for self-antigens recognized by pathogenic autoantibodies associated with the autoimmune disorder pemphigus vulgaris. Pemphaxin is believed to be one of the major proteins targeted by the autoimmune disorder. This corroborates the statement on page 7 of the Specification that the SEQ ID NO:12 polypeptide and the polynucleotides encoding it may be useful in the diagnosis and treatment of autoimmune disorders.

Applicants have previously argued that the annexin class of proteins have been found to be useful cell markers because of their phospholipid binding properties and their association with the plasma membrane (See the response to the Office Action of January 10, 2003 at page 22). However, the Examiner points out the absence of type II calcium binding sites in annexin 31, and argues that the SEQ ID NO:12 protein "would not have the phospholipid binding ability of other annexins" (Final Office Acton, page 22). Applicants disagree.

Other members of the annexin family display both calcium-dependent and calcium-independent binding to phospholipids. For example, annexin I has a calcium-independent form that associates with membranes in the absence of calcium. Phosphorylation of the calcium-independent form of annexin I by epidermal growth factor kinase converts annexin I to a calcium-dependent form that requires calcium for membrane association (See enclosed reference of Futter et al. (1993) J. Cell Biol. 120:77-83). Annexin II, annexin A11, and annexin XIII also are able to associate with membranes in the absence of calcium. (Also see the enclosed references of Jost et al. (1997) J. Cell Science 110:221-228, Lecona et al. (2003) Biochem. J. 373:437-449, and Lecat et al. (2000) J. Cell Science 113:2607-2618. Note, these references are submitted to rebut arguments made for the first time in the Final Office Action, and Applicants respectfully request that they be entered into the record.) Thus, the calcium binding site is not required in all annexins to confer phospholipid binding properties. The SEQ ID NO:12 polypeptide, as a member of the annexin family, more likely than not, is a phospholipid binding protein, and as such, is useful like other members of the annexin family.

The Office Action's argument amounts to nothing more than the Patent Office's disagreement with the Bedilion Declaration and the Applicants' assertions about the knowledge of a person of ordinary skill in the art, and is tantamount to the substitution of the Patent Office's own judgment for that of the Applicants' expert. The Patent Office is, moreover, wrong on the facts because the Bedilion Declaration demonstrates how one of skill in the art, reading the specification at the time the application was filed, would have understood that specification to disclose the use of SEQ ID NO:64 in gene expression monitoring for toxicology testing, drug development, and the diagnosis of disease (See the Bedilion Declaration at, e.g., ¶¶ 10-16).

II. Utility of the Claimed Polypeptides

In the Final Office Action, the Examiner agreed to rejoin claims 205-209, drawn to polypeptides of the invention. These claims were not previously included in the rejections under 35 U.S.C. §101 and §112, first paragraph in the Office Action of January 10, 2003. Their inclusion in the final rejection introduces new issues that are being addressed for the first time in the present Response.

As pointed out above, the Nguyen *et al.* article corroborates that the polypeptide of SEQ ID NO:12 is a member of the annexin family and is, in fact, the human keratinocyte annexin-like protein, Pemphaxin. Pemphaxin acts as a cell surface cholinergic receptor involved in the regulation of keratinocyte cell adhesion and known to be associated with the autoimmune disorder, pemphigus vulgaris. This also corroborates the statement on page 7 of the Specification that the SEQ ID NO:12 polypeptide and the polynucleotides encoding it may be useful in the diagnosis and treatment of autoimmune disorders.

In addition, Applicants are submitting with this paper a Declaration of Furness under 37 C.F.R. § 1.132 (the Furness Declaration) describing some of the practical uses of the claimed invention in protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic affect of a drug candidate. (Furness Declaration at ¶ 10).

The fact that the Furness Declaration is being submitted in response to positions taken and arguments made for the first time in the Final Office Action constitutes, by itself, "good and sufficient reasons" under 37 C.F.R. § 1.195 why that Declaration was not earlier submitted and should be admitted at this time.

In any event, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

The Patent Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the

claimed polypeptide cannot be useful without precise knowledge of its function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

A. The uses of INTRA for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Furness Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Yue '566 application on June 16, 1999 would have understood that application to disclose the claimed polypeptide to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 10-14). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 10.)

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or

states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Yue '566 application, the Wilkins article, and other related pre-June 1999 publications, persons skilled in the art on June 16, 1999 clearly would have understood the Yue '566 application to disclose the SEQ ID NO:12 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity . . . . (Furness Declaration, ¶10)
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> * * *
>
> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:12 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, p. 26).

B. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Furness in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, *et al.*, Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 1):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. ((Reference No. 1), page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, *et al.*, Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 2); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology - - potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 3).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 4) Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Yueier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The

implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

C. To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

CONCLUSION

Applicants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these

prior cases, "like a nose of wax,"[1] to target rejections of claims to polypeptide and polynucleotide sequences, as well as to claims to methods of detecting said polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

[1]"The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding **objections/rejections.** Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney/Agent below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**, as set forth in the enclosed fee transmittal letter.

Respectfully submitted,
INCYTE CORPORATION

Date: August 27, 2003

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Enclosures:
(A) list of cDNA libraries
(B) Nguyen *et al.* article
(C) Sequence Alignment
(D) Futter et al. (1993)
(E) Jost et al. (1997)
(F) Lecona et al. (2003)
(G) Lecat et al. (2000)